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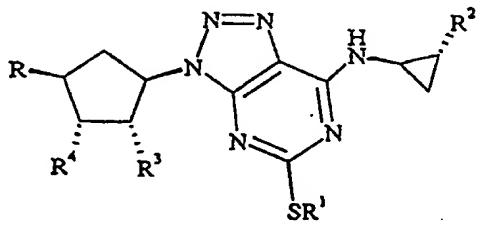
(54) Title: NOVEL TRIAZOLO(4,5-D)PYRIMIDINE COMPOUNDS



(I)

(57) Abstract

The invention provides new triazolo[4,5-*d*]pyrimidine compounds of formula (I), their use as medicaments, compositions containing them and processes for their preparation.

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NOVEL TRIAZOLO(4,5-D)PYRIMIDINE COMPOUNDS

FIELD OF THE INVENTION

The present invention provides new triazolo[4,5-*d*]pyrimidine compounds, their use as medicaments, compositions containing them and processes for their preparation.

BACKGROUND OF THE INVENTION

Platelet adhesion and aggregation are initiating events in arterial thrombosis. Although the process of platelet adhesion to the sub-endothelial surface may have an important role to play in the repair of damaged vessel walls, the platelet aggregation that this initiates can precipitate acute thrombotic occlusion of vital vascular beds, leading to events with high morbidity such as myocardial infarction and unstable angina. The success of interventions used to prevent or alleviate these conditions, such as thrombolysis and angioplasty is also compromised by platelet mediated occlusion or re-occlusion.

A number of converging pathways lead to platelet aggregation. Whatever the initial stimulus, the final common event is a cross-linking of platelets by binding of fibrinogen to a membrane-binding site, glycoprotein IIb/IIIa (GPIIb/IIIa). The high anti-platelet efficacy of antibodies or antagonists for GPIIb/IIIa is explained by their interference with this final common event. However, this efficacy may also explain the bleeding problems that have been observed with this class of agent. Thrombin can produce platelet aggregation largely independently of other pathways but substantial quantities of thrombin are unlikely to be present without prior activation of platelets by other mechanisms. Thrombin inhibitors such as hirudin are highly effective anti-thrombotic agents, but again may produce excessive bleeding because they function as both anti-platelet and anti-coagulant agents (The TIMI 9a Investigators (1994), *Circulation* **90**, pp. 1624-1630; The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators (1994) *Circulation* **90**, pp. 1631-1637; Neuhaus K.L. et. al. (1994) *Circulation* **90**, pp.1638-1642).

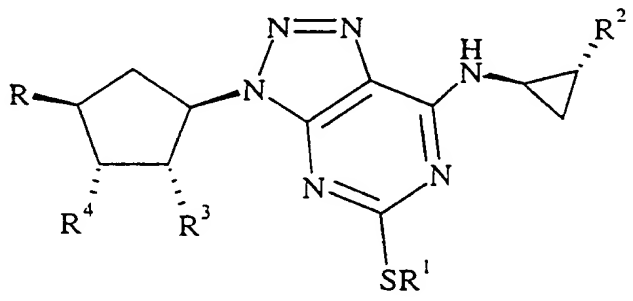
It has been found that adenosine 5'-diphosphate (ADP) acts as a key mediator of thrombosis. A pivotal role for ADP is supported by the fact that other agents, such as adrenaline and 5-hydroxytryptamine (5HT, serotonin) will only produce aggregation in the presence of ADP. The limited anti-thrombotic efficacy of aspirin may reflect the fact that it blocks only one source of ADP which is that released in a thromboxane-dependent manner following platelet adhesion (see e.g. Antiplatelet Trialists' Collaboration (1994), *Br. Med. J.* **308**, pp. 81-106 and Antiplatelet Trialists' Collaboration (1994), *Br. Med. J.* **308**, pp. 159-168). Aspirin has no effect on aggregation produced by other sources of ADP, such as damaged cells or ADP released under conditions of turbulent blood flow.

ADP-induced platelet aggregation is mediated by the P_{2T} receptor subtype located on the platelet membrane. The P_{2T} receptor (also known as $P2Y_{ADP}$ or $P2T_{AC}$) is primarily involved in mediating platelet aggregation/activation and is a G-protein coupled receptor which is as yet uncloned. The pharmacological characteristics of this receptor have been described, for example, in the references by Humphries et al., *Br. J. Pharmacology* (1994), **113**, 1057-1063, and Fagura et al., *Br. J. Pharmacology* (1998) **124**, 157-164. Recently it has been shown that antagonists at this receptor offer significant improvements over other anti-thrombotic agents (see *J. Med. Chem.* (1999) **42**, 213). Accordingly there is a need to find further P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) antagonists as anti-thrombotic agents.

International Patent Application WO 9905143 discloses generically a series of triazolo[4,5-*d*]pyrimidine compounds having activity as P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) antagonists. It has now been found that certain compounds within the scope of International Patent Application WO 9905143 but not specifically disclosed therein exhibit high potency combined with surprisingly high metabolic stability and bioavailibility, such that the predicted therapeutic dose for prolonged inhibition of aggregation in man shows advantage.

DESCRIPTION OF THE INVENTION

In a first aspect the invention therefore provides a compound of formula (I):



(I)

wherein:

R^1 is C_{3-5} alkyl optionally substituted by one or more halogen atoms;

R^2 is a phenyl group, optionally substituted by one or more fluorine atoms;

R^3 and R^4 are both hydroxy;

R is XOH, where X is CH_2, OCH_2CH_2 or a bond;

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

provided that:

when X is CH_2 or a bond, R^1 is not propyl.

when X is CH_2 and R^1 is $CH_2CH_2CF_3$, butyl or pentyl, the phenyl group at R^2 must be substituted by fluorine.

when X is OCH_2CH_2 and R^1 is propyl, the phenyl group at R^2 must be substituted by fluorine.

Alkyl groups, whether alone or as part of another group are straight chained and fully saturated.

Suitably R^1 is a C_{3-5} alkyl optionally substituted by one or more fluorine atoms. Preferably R^1 is C_{3-5} alkyl optionally substituted on the terminal carbon by three fluorine atoms. More preferably R^1 is 3,3,3,-trifluoropropyl, butyl or propyl.

Suitably R^2 is phenyl or phenyl substituted by one or more fluorine atoms. Preferably R^2 is phenyl, 4-fluorophenyl or 3,4-difluorophenyl.

Suitably R is XOH where X is CH_2, OCH_2CH_2 or a bond.

Preferably R is CH_2OH or OCH_2CH_2OH.

Particularly preferred compounds include:

[1*R*-[1α,2α,3β(1*R**,2*S**),5β]]-3-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol;

[1*R*-[1α,2α,3β(1*R**,2*S**),5β]]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol;

[1*S*-(1α, 2α, 3β (1*S**,2*R**),5β]]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol;

[1*R*-[1α,2α,3β(1*R**,2*S**),5β]]-3-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol;

[1*S*-[1α,2β,3β,4α(1*S**,2*R**)]]-4-[5-(Butylthio)-7-[[2-(4-fluorophenyl)cyclopropyl]amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-cyclopentane-1,2,3-triol;

[1*S*-(1α,2α,3β(1*S**,2*R**),5β)]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol;

[1*S*-[1α,2α,3β,5β(1*S**,2*R**)]]-3-(2-Hydroxyethoxy)-5-[7-(2-phenylcyclopropyl)amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-cyclopentane-1,2-diol

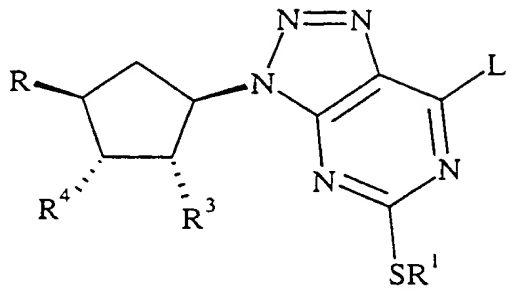
[1*S*-[1α,2β,3β,4α(1*S**, 2*R**)]]-4-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-1,2,3-triol;

[1*S*-[1α,2α,3β(1*S**,2*R**),5β]]-3-[5-(Butylthio)-7-[(2-phenylcyclopropyl)amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxethoxy)-cyclopentane-1,2-diol;

and pharmaceutically acceptable salts or solvates thereof, or solvates of such salts.

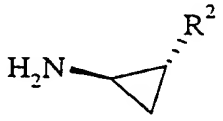
According to the invention there is further provided a process for the preparation of a compound of formula (I) which comprises:

(a) reacting a compound of formula (II):



(II)

where R, R^1, R^3 and R^4 are as defined in formula (I), or are protected derivatives thereof, or R^3 and R^4 together form a bond in the 5-membered ring, or R is CH_2CH_2OR', where R' is C_{1-6} alkyl or benzyl, and L is a leaving group such as halogen or SR, with a compound of formula (III):

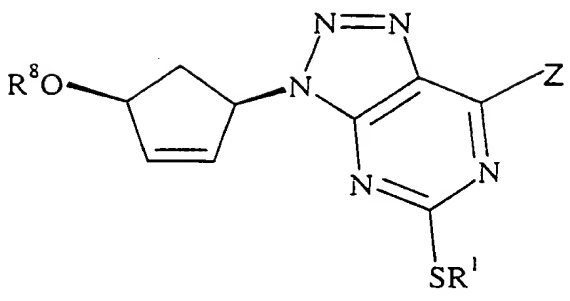


(III)

where R^2 is as defined in formula (I), or is a protected derivative thereof.

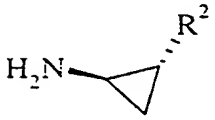
or where X is a bond:

(b) hydroxylation of a compound of formula (IV):



(IV)

where R^1 is defined in formula (I) and R^8 is H or $CH_2CH_2OP^3$ where P^3 is H or a protecting group or R^8 is CH_2COOR' where R' is C_{1-6} alkyl or benzyl, and Z is NH_2 or



where R^2 is defined in formula (I).

and for both (a) and (b) optionally thereafter and in any order:
converting one or more functional groups into further functional groups;
removing any protecting groups;
forming a pharmaceutically acceptable salt or solvate, or a solvate of such a salt.

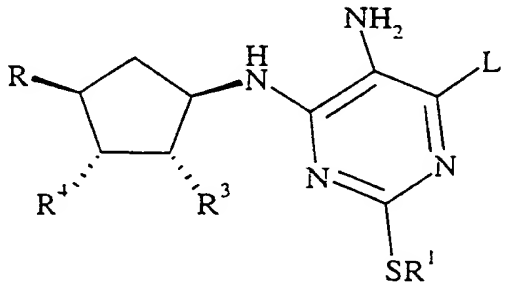
Compounds of formula (II) can be reacted with amines of formula (III) in the presence of a base, such as a tertiary organic amine, in an inert solvent, such as dichloromethane, at ambient or elevated temperature. Other suitable bases include inorganic bases such as potassium carbonate.

The hydroxy groups R^3 and R^4 can be protected as groups OP^1 and OP^2 where P^1 and P^2 are protecting groups. Examples of suitable protecting groups in compounds of formula (II) are C_{1-6} alkyl (preferably methyl), benzyl, $(C_{1-6}alkyl)_3Si$ (preferably t-butyldimethylsilyl), and a $C(O)C_{1-6}$alkyl group such as acetyl. Preferably the two groups P^1 and P^2 together with the atoms to which they are attached form an alkylidene ring such as a methylidene or isopropylidene ring. Alternatively P^1 and P^2 can form an alkoxymethylidene ring such as ethoxymethylidene.

Protecting groups can be added and removed using known reaction conditions. The use of protecting groups is fully described in 'Protective Groups in Organic Chemistry', edited by J W F McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T W Greene & P G M Wutz, Wiley-Interscience (1991).

Ester protecting groups can be removed by basic hydrolysis, for example by using a metal hydroxide, preferably an alkali metal hydroxide, such as sodium hydroxide or lithium hydroxide, or quaternary ammonium hydroxide in a solvent, such as aqueous ethanol or aqueous tetrahydrofuran, at a temperature of from 10° to 100°C, preferably the temperature is around room temperature; or by acidic hydrolysis using a mineral acid such as HCl or a strong organic acid such as trichloroacetic acid in a solvent such as aqueous 1,4-dioxane. Trialkylsilyl protecting groups can be removed by the use of, for example, a fluoride ion source, for example tetra-n-butylammonium fluoride or hydrogen fluoride. When one or both of P^1 and P^2 are C_{1-6} alkyl, deprotection can be achieved using boron tribromide. Benzyl groups can be removed by hydrogenolysis using a transition metal catalyst, for example palladium on charcoal, under an atmosphere of hydrogen, at a pressure of from 1 to 5 bar, in a solvent, such as acetic acid.

A compound of formula (II) can be prepared by diazotising a compound of formula (V):

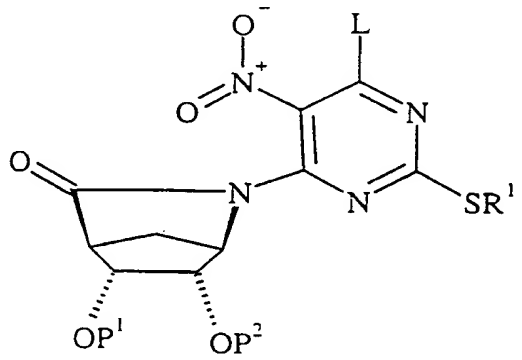


(V)

wherein R^1 is as defined in formula (I), and R is as defined in formula (I), or is a protected derivative thereof, or is OCH_2CO_2R', where R' is C_{1-6} alkyl or benzyl, and L is as defined

above and R^3 and R^4 are as defined in formula (I) or are protected derivatives thereof or R^3 and R^4 together form a bond in the 5-membered ring,
with a metal nitrite, for example an alkali metal nitrite, especially sodium nitrite in dilute aqueous acid, for example 2M HCl, or with a C_{1-6}-alkyl nitrite, in an inert solvent, at a temperature of from about -20 to about 100°C. Preferred conditions are isoamyl nitrite in acetonitrile at about 80°C.

A compound of formula (V) wherein R is CH_2OH, R^3 and R^4 are hydroxyl or protected derivatives thereof and L is as defined above, can be prepared by reducing a compound of formula (VI):



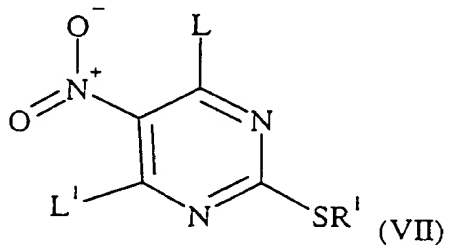
(VI)

wherein R^1, L, P^1 and P^2 are as defined above.

The reduction of the nitro group can be carried out for example by using hydrogenation with a transition metal catalyst at a temperature around room temperature, for example palladium on charcoal under an atmosphere of hydrogen, preferably at a pressure from 1 to 5 atmospheres, in a solvent, for example ethanol, or by using iron in an acidic solvent such as acetic acid at a temperature of about 100°C.

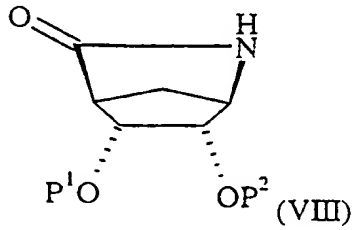
Reduction of the lactam can be carried out using complex metal hydrides such as lithium aluminium hydride in a solvent such as ether or preferably, by using sodium borohydride in a suitable solvent such as methanol.

A compound of formula (VI) can be prepared by reacting a compound of formula (VII):



(VII)

wherein L and R^1 are as defined above and L^1 is a leaving group, for example a halogen atom, wherein L and L^1 are preferably the same, with a compound of formula (VIII):



(VIII)

wherein P^1 and P^2 are as defined above, in the presence of a base such as C_{1-6}-alkyl-M or MH wherein M is a metal ion, for example n-butyl lithium, in an inert solvent, such as tetrahydrofuran, at a temperature of from about -10 to about 100°C. Preferably sodium hydride is used in tetrahydrofuran at room temperature.

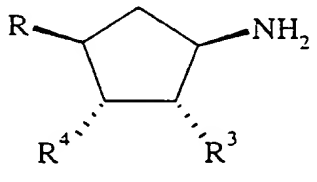
One or more functional groups can be converted into further functional groups using standard chemistry. A compound where X is a bond can be converted to a compound where X is $O(CH_2)_2$ by treatment with base followed by LY where L is a leaving group and Y is $(CH_2)_2OH$ or a protected version thereof or Y is CH_2COOR' where R' is C_{1-6} alkyl or benzyl. A compound where R is CH_2CH_2OR' may be converted into a compound where R is $O(CH_2)_2OH$ by reduction, for example using DIBAL-H® . The group SR^1 can be interconverted by oxidation of the sulfur, for example using oxone™ or mCBPA, followed by treatment with a compound $R^{1'}$-SM where $R^{1'}$ is a different R^1 group and M is a metal such as sodium. Alternatively the product of the sulfur oxidation may be treated with MSH

where M is a metal such as sodium, followed by treatment with a base and $R^{1'}X$ where $R^{1'}$ is a different R^1 group and X is a leaving group. Suitable bases include *N,N*-diisopropylethylamine.

A compound of formula (II) where R, R^1, R^3, and R^4 are as defined in formula (I) or are protected derivatives thereof. or R^3 and R^4 together form a bond in the 5-membered ring, or R is OCH_2CO_2R' where R' is C_{1-6} alkyl or benzyl, and L is a leaving group such as halogen, may be converted into a compound of formula (II) where R, R^1, R^3, and R^4 are defined above and L is NH_2 by treatment with a diazotizing agent in the presence of a halogenating agent, preferably isoamyl-nitrite and carbon tetrabromide.

A compound of formula (II) where R, R^1, R^3, and R^4 are defined above and L is NH_2 may be prepared by treating a compound of formula (II) where R, R^1, R^3, and R^4 are as defined above and L is a leaving group such as halogen, with ammonia in a solvent such as methanol.

Compounds of formula (V) can also be prepared by treating a compound of formula (XI)

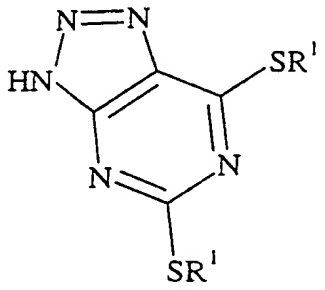


(XI)

where R, R^3 and R^4 are as defined in formula (I) or are protected derivatives thereof or R is OCH_2CO_2R' where R' is C_{1-6} alkyl or benzyl, or R^3 and R^4 together form a bond in the 5-membered ring,

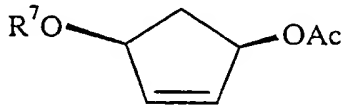
with a compound of formula (VII) as defined above, followed by reduction of the nitro group. The reaction is carried out in an inert solvent such as dichloromethane or 1,4-dioxane, in the presence of a non-nucleophilic base, such as *N,N*-diisopropylamine, at a tempeature of about -20°C to about 150°C, preferably at ambient temperature.

Compounds of formula (II) where R is as defined in formula (I), R^3 and R^4 together form a bond in the 5-membered ring, and L is SR^1, or a protected derivative thereof, can be prepared by reacting a compound of formula (XII):



(XII)

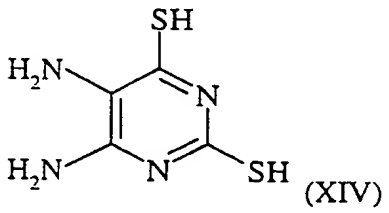
where R^1 groups are as defined in formula (I),
with a compound of formula (XIII):



(XIII)

in which R^7 is H or a protected derivative thereof. The reaction can be carried out in the presence of a suitable transition metal complex, preferably tetrakistriphenylphosphine palladium(0).

Compounds of formula (XII) can be prepared from compounds of formula (XIV):



(XIV)

by reacting with a compound R^1X where R^1 is as defined in formula (I) and X is a leaving group such as halo, followed by cyclisation.

Compounds of formula (XI) where R is OH or a protected version thereof and R^3 and R^4 are as defined in formula (I) or are protected derivatives thereof may be prepared from compounds of formula (XIII) where R^7 is H or a protecting group by treatment with a bisester of imidodicarbamic acid using palladium catalysis followed by hydroxylation of the double bond, and optionally, deprotection of the nitrogen. Preferably imidodicarbonic acid, bis-(1,1-dimethylethyl)ester and tetrakistriphenylphosphine palladium(0) are used followed by osmium tetroxide and deprotection using hydrochloric acid in methanol.

Compounds of formula (XI), where R is OCH_2CO_2R' where R' is C_{1-6} alkyl and R^3 and R^4 together form a bond in the 5-membered ring, may be formed from compounds of formula (XIII), where R^7 is H or a protecting group, by treatment with an azide in the presence of a palladium catalyst, followed by reduction of the azide and alkylation of the alcohol as described previously.

Compounds of formula (XI) where R is OCH_2CH_2OH and R^3 and R^4 are as defined in formula (I) or are protected derivatives thereof may be prepared from compounds of formula (XI) where R is OH and R^3 and R^4 are as defined in formula (I) or are protected derivatives thereof, by protection of the nitrogen, alkylation of the alcohol using a 2-halo-acetic acid ester, followed by reduction of the ester and deprotection of the nitrogen. We prefer protection of the nitrogen as a carbobenzyloxy derivative using benzyl chloroformate followed by alkylation of the alcohol using ethyl bromoacetate and potassium t-butoxide, reduction of the ester using lithium borohydride in tetrahydrofuran and deprotection of the nitrogen by hydrogenation in the presence of palladium on carbon. In addition we prefer the case where the alcohols R^3 and R^4 are protected as an isopropylidene ring.

The amines of formula (III) can be prepared using procedures described in H Nishiyama *et al*, Bull. Chem. Soc., Jpn., 1995, **68**, 1247, P. Newman, Optical Resolution Procedures for Chemical Compounds, Vol. 1, Amines and Related Compounds; Optical Resolution and

Information Centre: Manhattan College, Riverdale, NY, 1978, p120, J. Vallgarda *et al*, J. Chem. Soc. Perkin 1, 1994, 461 or in International Patent Application WO 9905143.

All novel intermediates form a further aspect of the invention.

Salts of the compounds of formula (I) may be formed by reacting the free acid, or a salt thereof, or the free base, or a salt or a derivative thereof, with one or more equivalents of the appropriate base (for example ammonium hydroxide optionally substituted by C_{1-6}-alkyl or an alkali metal or alkaline earth metal hydroxide) or acid (for example a hydrohalic (especially HCl), sulphuric, oxalic or phosphoric acid). The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g. water, ethanol, tetrahydrofuran or diethyl ether, which may be removed *in vacuo*, or by freeze drying. The reaction may also be a metathetical process or it may be carried out on an ion exchange resin. The non-toxic physiologically acceptable salts are preferred, although other salts may be useful, e.g. in isolating or purifying the product.

The compounds of the invention act as P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) receptor antagonists. Accordingly, the compounds are useful in therapy, including combination therapy, particularly they are indicated for use as: inhibitors of platelet activation, aggregation and degranulation, promoters of platelet disaggregation, anti-thrombotic agents or in the treatment or prophylaxis of unstable angina, primary arterial thrombotic complications of atherosclerosis such as thrombotic or embolic stroke, transient ischaemic attacks, peripheral vascular disease, myocardial infarction with or without thrombolysis, arterial complications due to interventions in atherosclerotic disease such as angioplasty, including coronary angioplasty (PTCA), endarterectomy, stent placement, coronary and other vascular graft surgery, thrombotic complications of surgical or mechanical damage such as tissue salvage following accidental or surgical trauma, reconstructive surgery including skin and muscle flaps, conditions with a diffuse thrombotic/platelet consumption component such as disseminated intravascular coagulation, thrombotic thrombocytopaenic purpura, haemolytic uraemic syndrome, thrombotic complications of septicaemia, adult respiratory distress syndrome, anti-phospholipid syndrome, heparin-induced

thrombocytopaenia and pre-eclampsia/eclampsia, or venous thrombosis such as deep vein thrombosis, venoocclusive disease, haematological conditions such as myeloproliferative disease, including thrombocythaemia, sickle cell disease; or in the prevention of mechanically-induced platelet activation *in vivo*, such as cardio-pulmonary bypass and extracorporeal membrane oxygenation (prevention of microthromboembolism), mechanically-induced platelet activation *in vitro*, such as use in the preservation of blood products, e.g. platelet concentrates, or shunt occlusion such as in renal dialysis and plasmapheresis, thrombosis secondary to vascular damage/inflammation such as vasculitis, arteritis, glomerulonephritis, inflammatory bowel disease and organ graft rejection, conditions such as migraine, Raynaud's phenomenon, conditions in which platelets can contribute to the underlying inflammatory disease process in the vascular wall such as atheromatous plaque formation/progression, stenosis/restenosis and in other inflammatory conditions such as asthma, in which platelets and platelet-derived factors are implicated in the immunological disease process. Further indications include treatment of CNS disorders and prevention of the growth and spread of tumours.

According to the invention there is further provided the use of a compound according to the invention as an active ingredient in the manufacture of a medicament for use in the treatment or prevention of the above disorders. In particular the compounds of the invention are useful for treating myocardial infarction, thrombotic stroke, transient ischaemic attacks, peripheral vascular disease and stable and unstable angina, especially unstable angina. The invention also provides a method of treatment or prevention of the above disorders which comprises administering to a person suffering from or susceptible to such a disorder a therapeutically effective amount of a compound according to the invention.

The compounds may be administered topically, e.g. to the lung and/or the airways, in the form of solutions, suspensions, HFA aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, pills, capsules, syrups, powders or granules, or by parenteral administration in the form of sterile parenteral solutions or suspensions, by subcutaneous administration, or by rectal administration in the

form of suppositories or transdermally.

The compounds of the invention may be administered on their own or as a pharmaceutical composition comprising the compound of the invention in combination with a pharmaceutically acceptable diluent, adjuvant and/or carrier. Particularly preferred are compositions not containing material capable of causing an adverse, e.g. an allergic, reaction.

Dry powder formulations and pressurised HFA aerosols of the compounds of the invention may be administered by oral or nasal inhalation. For inhalation the compound is desirably finely divided. The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

One possibility is to mix the finely divided compound with a carrier substance, e.g. a mono-, di- or polysaccharide, a sugar alcohol or another polyol. Suitable carriers include sugars and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, e.g. that known as the Turbuhaler® in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active compound with or without a carrier substance is delivered to the patient.

The pharmaceutical composition comprising the compound of the invention may conveniently be tablets, pills, capsules, syrups, powders or granules for oral administration; sterile parenteral or subcutaneous solutions, suspensions for parenteral administration or suppositories for rectal administration.

For oral administration the active compound may be admixed with an adjuvant or a carrier, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatine or polyvinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet may be coated with a suitable polymer dissolved either in a readily volatile organic solvent or an aqueous solvent.

For the preparation of soft gelatine capsules, the compound may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above mentioned excipients for tablets, e.g. lactose, saccharose, sorbitol, mannitol, starches, cellulose derivatives or gelatine. Also liquid or semisolid formulations of the drug may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing the compound, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

EXAMPLES

The invention is illustrated by the following non-limiting examples.

In the examples the NMR spectra were measured on a Varian Unity Inova 300 or 400 spectrometer and the MS spectra were measured as follows: EI spectra were obtained on a VG 70-250S or Finnigan Mat Incos-XL spectrometer, FAB spectra were obtained on a VG70-250SEQ spectrometer, ESI and APCI spectra were obtained on Finnigan Mat SSQ7000 or a Micromass Platform spectrometer. Preparative HPLC separations were

generally performed using a Novapak®, Bondapak® or Hypersil® column packed with BDSC-18 reverse phase silica. Flash chromatography (indicated in the Examples as (SiO_2)) was carried out using Fisher Matrix silica, 35-70 μm. For examples which showed the presence of rotamers in the proton NMR spectra only the chemical shifts of the major rotamer are quoted.

Example 1

[1*R*-[1α,2α,3β(1*R,2*S**),5β]]-3-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol**

a) [3a*S*-[1(*E*),3aα,6α,7aβ]]-1-[3-(4-Fluorophenyl)-1-oxo-2-propenyl]-hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide

A mixture of 3-(4-fluorophenyl)-2-propenoic acid (3.0g) and thionyl chloride (5.0ml) was stirred at 70°C for 1 hour, the reaction mixture was then concentrated under reduced pressure. The residue was azeotroped twice with dichloromethane then dissolved in toluene (10ml). To a suspension of sodium hydride (60% dispersion in oil; 0.99g) in toluene (40ml) was added a solution of [3a*S*-(3aα,6α,7aβ)]-hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide (3.89g) in toluene (40ml) and the mixture stirred for 30 minutes. To the reaction mixture was then added the solution described above and the resulting suspension was stirred for 16 hours. Water (200ml) was added. the organics collected and the aqueous extracted into dichloromethane (3x100ml). The organics were combined, dried and concentrated. Recrystallisation (ethanol) gave the subtitle compound as colourless needles (5.92g).

MS (APCI) 364 ($M+H^+$,100%)

b) [3a*S*-[1(1*S,2*S**),3aα,6α,7aβ]]-1-[[2-(4-Fluorophenyl)cyclopropyl]carbonyl]-hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide**

A solution of diazomethane (2.9g) in ether (150ml) (prepared as described in Vogel's Textbook of Practical Organic Chemistry, Fifth Edition, Longman Scientific and Technical, p432) was added to a solution of the product of step a) (5.90g) and palladium(II) acetate (18mg) in dichloromethane (350ml) at 0°C and the reaction mixture stirred at 0°C for 5 hours. Acetic acid (5ml) was added and the reaction mixture was then washed with saturated sodium bicarbonate solution (200ml) and the organics filtered through a plug of silica. After concentrating *in vacuo*, the residue was recrystallised (ethanol) to give the subtitle compound as colourless needles (3.81g).

MS (APCI) 378 ($M+H^+$,100%)

c) (1*R-trans*)-2-(4-Fluorophenyl)-cyclopropanecarboxylic acid

A suspension of the product from step b) (3.74g) and lithium hydroxide monohydrate (4.11g) in tetrahydrofuran (100ml)/ water (3ml) was stirred at 50°C for 24 hours. The reaction mixture was concentrated *in vacuo*, and the residue dissolved in water (100ml), acidified with 2N HCl and extracted into dichloromethane (3x75ml). The organics were dried and concentrated. Purification (SiO_2, isohexane:diethylether 2:1 as eluant) gave the subtitle compound as a colourless solid (1.78g).

MS (APCI) 179 ($M-H^+$,100%)

d) (1*R-trans*)-2-(4-Fluorophenyl)cyclopropanamine, [*R*-(*R,*R**)]-2,3-dihydroxybutanedioate (1:1)**

To a solution of the product from step c) (1.78g) and triethylamine (2.7ml) in acetone /water (10:1, 23ml) at 0 °C was added ethyl chloroformate (2.0ml) over 5 min. The solution was maintained at 0 °C for 30 minutes before addition of sodium azide (1.52g) in water (6ml). After a further hour, water (350ml) was added and the reaction mixture extracted with toluene (3x100ml). The organic extracts were combined and dried, then heated at reflux for 2 hours behind a blast screen. After cooling the solution, 6N HCl

(50ml) was added and the mixture heated at reflux for 3 hours. Water (150ml) was added and the aqueous phase basified with 2N NaOH (aq), then extracted into dichloromethane (3x100ml). The organic phase was dried and concentrated. The amine was dissolved in ethanol (5ml) and a solution of L-tartaric acid (1.48g) in ethanol (20ml) was added. After 20 minutes the solid was collected affording the subtitle compound as colourless needles (1.12g).

NMR δH (d_6-DMSO) 1.07-1.39 (1H, m), 1.22-1.29 (1H, m), 2.16-2.23 (1H, m), 2.64-2.70 (1H,m), 3.95 (2H, s), 7.06-7.19 (4H, m)

e) [3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]]-6-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol**

N,*N*-Diisopropylethylamine (1.29g) was added to a solution of [3a*R*-(3aα,4α,6α,6aα)]-6-[7-chloro-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol (prepared as described in International Patent Application WO 9703084) (1.0g) and the product of step d) (0.75g) in dichloromethane (25ml). The reaction mixture was stirred at room temperature for 3 hours, then washed with water, dried and evaporated. The residue was purified (SiO_2, ethyl acetate:isohexane 1:1 as eluent) to afford the subtitle compound (1.25g).

MS (APCI) 515 ($M+H^+$, 100%)

f) [3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]]-6-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-(propylsulphonyl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol**

3-Chloroperoxybenzoic acid (70%, 1.8g) was added to a suspension of the product of step e) (1.25g) in ethanol (25ml) and the resulting solution stirred at room temperature for 2 hours. The reaction mixture was concentrated and the residue taken up in ethyl acetate

(500ml), washed with 10% aqueous sodium metabisulfite solution (2 x 100ml) and 10% aqueous sodium bicarbonate solution (2x100ml) then dried and concentrated to afford the subtitle compound (1.4g).

MS (APCI) 547 ($M+H^+$, 100%)

g) [[3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]]-6-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropy)lthio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol**

Sodium hydrosulfide hydrate (1.4g) was added to a solution of the product of step f) (1.4g) in dimethyl sulphoxide (20ml) and the solution stirred at room temperature for 1.5 hours. Brine (150ml) was added and the mixture acidified with acetic acid then extracted with ethyl acetate (3x100ml). The organic phase was dried and concentrated and the residue azeotroped with toluene (3x100ml). The residue was dissolved in *N,N*-dimethylformamide (20ml) then *N,N*-diisopropylethylamine (0.33g) and 3,3,3-trifluoropropylbromide (0.48g) added. After stirring at 50°C for 30 minutes the reaction mixture was diluted with ethyl acetate (100ml) then washed with aqueous brine (3x100ml), dried and concentrated then the residue purified (SiO_2, isohexane:ethyl acetate 1:1 as eluant) to afford the subtitle compound (1.4g).

MS (APCI) 569 ($M+H^+$, 100%)

h) [1*R*-[1α,2α,3β(1*R,2*S**),5β]]-3-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol**

A solution of the product from step g) (1.4g) in trifluoroacetic acid (10ml) and water (2ml) was stirred at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate (400ml) then washed with sodium bicarbonate solution (400ml), dried and

evaporated. The residue was purified (SiO_2, methanol:chloroform 3:47 as eluant) to afford the title compound (0.44g).

MS (APCI) 529 ($M+H^+$,100%)

NMR δH (d_6-DMSO) 9.42 (1H, d), 7.27-7.22 (2H, m), 7.14-7.08 (2H, m), 5.01-4.95 (2H, m), 4.73-4.70 (2H, m), 4.44-4.41 (1H, m), 3.87-3.84 (1H, m), 3.50-3.45 (2H, m), 3.26-3.13 (3H, m), 2.60-2.55 (1H, m), 2.28-2.20 (2H, m), 2.10-2.06 (1H, m), 1.90-1.80 (1H, m), 1.49-1.46 (1H, m), 1.33-1.30 (1H, m).

Example 2

[1*R*-[1α,2α,3β(1*R,2*S**),5β]]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol**

a) **[3a*S*-[1(*E*),3aα,6α,7aβ]]-1-[3-(3,4-Difluorophenyl)-1-oxo-2-propenyl]-hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide**

The subtitle compound was prepared according to the method of Example 1, step a) using 3-(3,4-difluorophenyl)-2-propenoic acid.

MS (APCI) 382 ($M+H^+$, 100%)

b) **[3a*S*-[1(1*S**,2*S**),3aα,6α,7aβ]]-1-[[2-(3,4-Difluorophenyl)cyclopropyl]carbonyl]-hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide**

The subtitle compound was prepared according to the method of Example 1, step b) using the product of step a).

MS (APCI) 396 ($M+H^+$, 100%)

c)(1*R-trans*)-2-(3,4-Difluorophenyl)-cyclopropane carboxylic acid

The subtitle compound was prepared according to the method of Example 1, step c) using the product of step b).

NMR δH ($CDCl_3$) 7.06 (1H, dt, *J*=10.0, *J*=8.5 Hz), 6.93-6.80 (2H, m), 2.58-2.52 (1H, m), 1.88-1.82 (1H, m), 1.66 (1H,dt, *J*=9.2, *J*=5.2 Hz), 1.34 (1H, ddd, *J*=8.5, *J*=6.5, *J*=4.8 Hz).

d)(1*R-trans*)-2-(3,4-Difluorophenyl)cyclopropanamine, [*R*-(*R,*R**)]-2,3-dihydroxybutanedioate (1:1)**

The subtitle compound was prepared according to the method of Example 1, step d) using the product of step c).

MS (APCI) 170 ($M+H^+$, 100%)

e)[3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]-6-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol**

Isoamyl nitrite (5.1ml) was added to a solution of [3a*R*-(3aα,4α,6α,6aα)]-6-[[5-amino-6-Chloro-2-[(3,3,3-trifluoropropyl)thio]-4-pyrimidinyl]-amino]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol (prepared as described in International Patent Application WO 9703084) (8.1g) in acetonitrile (1000ml) and the solution heated at 70°C for 1 hour. The cooled reaction mixture was concentrated and purified (SiO_2, dichloromethane:ethyl acetate 4:1 as eluant) to afford an intermediate which was converted to the subtitle compound by the method of example 1, step e) using the product of step d).

MS (APCI) 587 ($M+H^+$, 100%)

f) [1*R*-[1α,2α,3β(1*R,2*S**),5β]]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol**

Prepared according to the method of example 1, step h) using the product of step e).

MS (APCI) 547 ($M+H^+$, 100%)

NMR δH (d_6-DMSO) 9.43 (1H, d), 7.35-7.28 (2H, m), 7.14-7.02 (1H, m), 5.01-4.96 (2H, m), 4.72-4.69 (2H, m), 4.42 (1H, q), 3.87-3.84 (1H, m), 3.50-3.44 (2H, m), 3.25-3.12 (3H, m), 2.58-2.50 (2H, m), 2.28-2.21 (3H, m), 1.85-1.80 (1H, m), 1.52-1.50 (1H, m), 1.39-1.37 (1H, m).

Example 3

[1*S*-(1α, 2α, 3β (1*S,2*R**),5β)]-3-[7-[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol,**

a) (1*R*-*cis*)-Bis(1,1-dimethylethyl)-4-hydroxy-2-cyclopentenylimidodicarbonate

To a suspension of ether washed sodium hydride (60% dispersion in oil; 0.31g) in tetrahydrofuran (30ml) was added imidodicarbonic acid bis-(1,1-dimethylethyl)ester (1.84g). The mixture was stirred at 40°C for 1 hour. To the mixture, at ambient temperature, was then added (1*S*-*cis*)-4-acetoxy-2-cyclopenten-1-ol (0.5g) and tetrakis(triphenylphosphine)palladium(0) (0.18g). The reaction mixture was stirred for 24 hours then purified (SiO_2, ethyl acetate: hexane 1:9 as eluant) to give the subtitle compound as a colourless solid (0.90g).

NMR δH (d_6-DMSO) 1.43 (18H, s), 1.61 (1H, ddd, *J*=12.3, 7.7, 6.4 Hz), 2.54 (1H, dt, *J*=12.6, 7.4 Hz), 4.51-4.57 (1H, m), 4.86 (1H, tq, *J*=8.0, 1.8 Hz), 4.91 (1H, d, *J*=5.4 Hz), 5.71-5.77 (2H, m).

b) [1*R*-(1α,2β,3β,4α)]-2,3,4-Trihydroxy-cyclopentenylimidodicarbonic acid, bis(1,1-dimethylethyl) ester

To a solution of the product of step a) (17.1g) in tetrahydrofuran (500ml)/water (50ml) was added *N*-methylmorpholine-*N*-oxide (9.4g) followed by osmium tetroxide (10ml, 2.5% solution in *t*-butanol). The mixture was stirred at room temperature for 4 days then treated with sodium hydrosulphite (6.0g). The suspension was filtered through celite and the product purified (SiO_2, ethyl acetate: hexane 1:1 as eluant) to afford the subtitle compound (19.1g).

NMR δH (d_6-DMSO) 1.44 (18H, s), 1.46-1.60 (1H, m), 1.97-2.05 (1H, m), 3.55-3.58 (1H, m), 3.66-3.73 (1H, m), 4.11-4.21 (2H, m), 4.54 (1H, d, *J*=4.8 Hz), 4.56 (1H, d, *J*=5.9 Hz), 4.82 (1H, d, *J*=4.6 Hz)

c) [3a*R*-(3aα,4α,6α,6aα)]-6-Amino-tetrahydro-2,2-dimethyl- 4*H*-cyclopenta-1,3-dioxol-4-ol, hydrochloride

The product from step b) (17.4g) in 6M HCl (100ml)/methanol (500ml) was stirred for 18 hours. The mixture was evaporated and then azeotroped with toluene (4 x 200ml) to give a colourless powder (8.7g). This solid was suspended in acetone (250ml) containing 2,2-dimethoxypropane (25ml) and cHCl (0.2ml) then heated under reflux for 2 hours. The mixture was cooled, evaporated and azeotroped with toluene (3 x 200ml). The residue was dissolved in 20% aqueous acetic acid and stirred for 2 hours. The mixture was evaporated and azeotroped with toluene (4 x 200ml) to afford the subtitle compound (10.1g).

MS (APCI) 174 ($M+H^+$, 100%)

d) [3a*R*-(3aα,4α,6α,6aα)]-6-[[6-Chloro-5-nitro-2-(propylthio)-pyrimidin-4-yl]amino]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-ol

A solution of the product from step c) (10.0g) and *N,N*-diisopropylethylamine (35ml) in tetrahydrofuran (600ml) was stirred for 1 hour. The mixture was filtered and the solution was added over 1 hour to a solution of 4,6-dichloro-5-nitro-2-(propylthio)-pyrimidine (prepared as described in International Patent Application WO 9703084) (25.6g) in tetrahydrofuran (1000ml) and stirred for a further 2 hours. The solvent volume was reduced *in vacuo* and ethyl acetate was added (1000ml). The mixture was washed with water and the organic layers were dried, evaporated and purified (SiO_2, isohexane-ethyl acetate as eluant) to afford the subtitle compound (14.2g).

MS (APCI) 405 ($M+H^+$, 100%)

e) [3a*R*-(3aα,4α,6α,6aα)]-6-[[5-Amino-6-Chloro-2-(propylthio)-pyrimidin-4-yl]amino]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-ol

Iron powder (3.0g) was added to a stirred solution of the product of step d) (2.7g) in acetic acid (100ml). The reaction mixture was stirred at room temperature for 2 hours, concentrated to half volume, diluted with ethyl acetate and washed with water. The organic phase was dried and concentrated to afford the subtitle compound (2.0g).

MS (APCI) 375 ($M+H^+$, 100%)

f) [3a*R*-(3aα,4α,6α,6aα)]-6-[7-Chloro-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-ol

Isoamyl nitrite (1.1ml) was added to a solution of the product of step e) (2.0g) in acetonitrile (100ml) and the solution heated at 70°C for 1 hour. The cooled reaction mixture was concentrated and purified (SiO_2, ethyl acetate:isohexane 1:3 as eluant) to afford the subtitle compound (1.9g).

MS (APCI) 386 ($M+H^+$, 100%)

g) [3a*R*-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-ol

The product of step f) (13.2g) in tetrahydrofuran (200ml) containing 0.88 ammonia (5ml) was stirred for 2 hours then concentrated to dryness and the residue partitioned between water and ethyl acetate. The organics were dried and then concentrated to afford the subtitle compound (12.5g).

MS (APCI) 367 ($M+H^+$, 100%).

h) [3a*R*-(3aα,4α,6α,6aα)]-[[6-[7-Amino-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-ol]oxy]acetic acid, methyl ester

To a solution of the product of step g) (0.50g) in tetrahydrofuran (25ml) at 0°C, was added butyllithium (0.62ml of 2.5N in hexanes). After 20 minutes, the suspension was treated with a solution of trifluoromethanesulfonyloxy-acetic acid methyl ester (0.34g) (prepared according to the method of Biton, Tetrahedron, 1995, **51**, 10513) in tetrahydrofuran (10ml). The resulting solution was allowed to warm to room temperature then concentrated and purified (SiO_2, ethyl acetate: hexane 4:6 as eluant) to afford the subtitle compound (0.25g).

MS (APCI) 439 ($M+H^+$, 100%).

i) [3a*R*-(3aα,4α,6α,6aα)]-[[6-[7-Bromo-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-ol]oxy]acetic acid, methyl ester

The product from step h) (1.1g) and isoamylnitrite (2.4ml) in bromoform (30ml) was heated at 80°C for 30 minutes . The cooled reaction mixture was purified (SiO_2, ethyl acetate:isohexane 1:4 as eluant) to afford the subtitle compound (0.44g).

MS (APCI) 502/4 ($M+H^+$), 504 (100%).

j) [3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]]-[[6-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-yl]oxy]acetic acid, methyl ester**

To a mixture of the products from step i) (0.80g) and Example 2, step d) (0.61g) in dichloromethane (25ml) was added *N,N*-diisopropylethylamine (0.85ml). The resulting solution was stirred at room temperature for 16 hours then concentrated *in vacuo*. Purification (SiO_2, isohexane:ethylacetate 3:1 as eluant) gave the subtitle compound as a colourless foam (0.77g).

MS (APCI) 591 ($M+H^+$, 100%)

k) [3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]]-2-[6-[[7-[2-(3,4-Difluorophenyl) cyclopropyl]amino-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-yl]oxy]-ethanol**

DIBAL-H® (1.0M solution in hexanes, 5.15ml) was added to an ice-cooled solution of the product of step j) (0.76g) in tetrahydrofuran (1ml) and the solution stirred at this temperature for 2 hours. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate (75ml). A saturated aqueous solution of sodium potassium tartrate (75ml) was added and the mixture stirred vigorously for 16 hours. The organics were collected and the aqueous re-extracted with ethyl acetate (2x50 ml). The combined organics were dried and concentrated and the residue purified (SiO_2, isohexane:ethylacetate 1:1 as eluant) to give the subtitle compound (0.63g).

MS (APCI) 563 ($M+H^+$,100%)

l) [1S-[1α,2α,3β(1S*,2R*),5β]]-3-[7-(2-(3,4-Difluorophenyl)cyclopropylamino)-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol

Prepared according to the method of example 1, step h) using the product of step k).

MS (APCI) 523 ($M+H^+$, 100%)

NMR δH (d_6-DMSO) 8.95 (1H, d, *J*=3.3 Hz), 7.39-7.21 (2H, m), 7.10-7.00 (1H, m), 5.12 (1H, d, *J*=6.4 Hz), 5.05 (1H, d, *J*=3.6 Hz), 4.96 (1H, q, *J*=9.0 Hz), 4.62-4.54 (2H, m), 3.95 (1H, br s), 3.79-3.73 (1H, m), 3.55-3.47 (4H, m), 3.20-3.13 (1H, m), 2.98-2.81 (2H, m), 2.63 (1H, dt, *J*=13.6, 8.5 Hz), 2.29-2.21 and 2.16-2.09 (1H, m), 2.07-2.00 (1H, m), 1.73-1.33 (4H, m), 0.99 (3H, t, *J*=7.4 Hz).

Example 4

[1*R*-[1α,2α,3β(1*R,2*S**),5β]]-3-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol**

a) **[3a*R*-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol**

Prepared according to the method of Example 3, step g) using [3a*R*-(3aα,4α,6α,6aα)]-6-[7-chloro-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol (prepared as described in International Patent Application WO 9703084). The crude product was purified (SiO_2, methanol:dichloromethane 1:19 as eluant) to give the subtitle compound.

MS (APCI) 381 ($M+H^+$, 100%).

b) [3a*R*-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(propylsulfonyl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol

Prepared according to the method of example 1, step f) using the product of step a).

MS (APCI) 413 ($M+H^+$, 100%).

c) [3a*R*-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(butylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol

1-Butanethiol (2.38ml) in DMF (25ml) was added to a suspension of sodium hydride (60%, 1.09g) in DMF (50ml). After 1 hour a solution of the product of step b) (3.66g) in DMF (65ml) was added dropwise and the resulting mixture was stirred overnight. The reaction mixture was added slowly to saturated aqueous sodium bicarbonate (1000ml) and then extracted into ethyl acetate (3 x 200ml). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* and the residue purified (SiO_2, methanol:dichloromethane 1:19 as eluant) to give the subtitle compound (3.32g).

MS (APCI) 395 ($M+H^+$, 100%).

d) [3a*R*-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(butylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol, acetate

To a solution of the product from step c) (3.3g) in dichloromethane (50ml), was added pyridine (2.7ml), 4-dimethylaminopyridine (0.4g) and acetic anhydride (2.0 ml). The mixture was stirred at room temperature overnight, concentrated *in-vacuo* and purified (SiO_2, diethyl ether:isohexane 3:2 as eluent) to give the subtitle compound (2.7g).

MS (APCI) 437 ($M+H^+$, 100%).

e) [3a*R*-(3aα,4α,6α,6aα)]-6-[7-Bromo-5-(butylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol, acetate

Prepared according to the method of example 3, step i) using the product of step d).

MS (APCI) 500/502 ($M+H^+$), 500 (100%).

f) [3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]]-6-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol, acetate**

Prepared according to the method of example 3, step j) using the product of example 2, step d) and the product of step e).

MS (APCI) 589 ($M+H^+$, 100%).

g) [1*R*-[1α,2α,3β(1*R,2*S**),5β]]-3-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol**

The product of step f) (0.64g) in 80% aqueous acetic acid (30ml) was heated at 80°C for 1 hour. The cooled mixture was poured into saturated sodium bicarbonate solution and extracted into ethyl acetate. The organic phase was dried and concentrated *in vacuo* to give a gum which was dissolved in methanol (50ml)/10% aqueous potassium carbonate solution (3ml). The solution was stirred for 30 minutes, neutralised with acetic acid, and concentrated *in vacuo*. Purification (SiO_2, methanol:dichloromethane 1:19 as eluent) gave a solid which was recrystallised (acetonitrile) to give the title compound (0.25g).

MS (APCI) 507 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 9.34 (1H, br), 7.40-7.23 (2H, m), 7.11-7.00 (1H, m), 5.06-4.93 (2H, m), 4.76-4.67 (2H, m), 4.48-4.38 (1H, m), 3.91-3.84 (1H, m), 3.56-3.39 (2H, m), 3.21-3.08 (1H, m), 3.03-2.83 (2H, m), 2.32-2.17 (1H, m), 2.17-2.03 (2H, m), 1.91-1.77 (1H, m), 1.71-1.32 (4H, m), 1.32-1.17 (2H, m), 0.81 (3H, t).

Example 5

[1*S*-[1α,2β,3β,4α(1*S,2*R**)]]-4-[5-(Butylthio)-7-[[2-(4-fluorophenyl)cyclopropyl]amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-cyclopentane-1,2,3-triol**

a) [3a*R*-[3aα,4α,6α,6aα(1*S,2*R**)]]-6-[7-[[(4-Fluorophenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-ol**

Prepared according to the method of example 1, step e) using the product of example 1, step d) and the product of example 3 step f).

MS (APCI) 501 ($M+H^+$, 100%).

b) [3a*R*-[3aα,4α,6α,6aα(1*S,2*R**)]]-6-[[7-[(4-Fluorophenyl)cyclopropyl]amino]-5-(propylsulphonyl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-ol**

Prepared according to the method of example 1, step f) using the product of step a).

MS (APCI) 532 ($M+H^+$, 100%).

c) [3a*R*-[3aα,4α,6α,6aα(1*S,2*R**)]]-6-[7-[[(4-Fluorophenyl)cyclopropyl]amino]-5-(butylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-ol**

Prepared according to the method of example 4 step c) using the product of step b).

MS (APCI) 515 ($M+H^+$, 100%).

[1*S*-[1α,2β,3β,4α(1*S,2*R**)]]-4-[5-(Butylthio)-7-[[2-(4-fluorophenyl)cyclopropyl]amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-cyclopentane-1,2,3-triol**

Prepared according to the method of example 1 step h) using the product of step c).

MS (APCI) 575 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 7.26-7.22 (2H, m), 7.11 (2H, t), 4.99-4.90 (1H, m), 4.67-4.63 (1H, m), 3.93 (1H, s), 3.77 (1H, bs), 3.35-3.13 (1H, m), 3.00-2.80 (2H, m), 2.59-2.51 (1H, m), 2.15-2.11 (1H, m), 1.91-1.86 (1H, m), 1.53-1.41 (3H, m), 1.35-1.30 (1H, m), 1.22 (2H, sex), 0.80 (3H, t).

Example 6

[1*S*-(1α,2α,3β(1*S,2*R**),5β)]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol**

a) **[1*S*-(1α,2α,3β(1*S**,2*R**),5β)]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylsulphonyl)-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol**

The subtitle compound was prepared according to the method of Example 1, step f) using the product of Example 3, step l.

MS(APCI) 555($M+H^+$, 100%)

b) [1*S*-(1α,2α,3β(1*S,2*R**),5β)]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol**

The title compound was prepared according to the method of Example 1, step g) using the product of step a).

MS(APCI) 555 ($M+H^+$, 100%)

NMR δH (d_6-DMSO) 9.45 (1H. d), 7.36-7.05 (3H, m), 5.05 (1H, d), 5.02 (1H, d), 4.95 (1H, m), 4.60 (2H, m), 3.95 (1H, m), 3.86 (1H, m), 3.47 (4H, m), 3.30-3.11 (3H, m), 2.63-2.49 (3H, m), 2.19 (1H, m), 2.00 (1H, m), 1.53 (1H, m), 1.40 (1H, m).

Example 7

[1*S*-[1α,2α,3β,5β(1*S,2*R**)]]-3-(2-Hydroxyethoxy)-5-[7-(2-phenylcyclopropyl)amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-cyclopentane-1,2-diol**

a) (1*S*-*cis*)-2-[[4-[[6-Chloro-5-nitro-2-[(3,3,3-trifluoropropyl)thio]-4-pyrimidinyl]amino]-2-cyclopenten-1-yl]oxy]-acetic acid, ethyl ester

A solution of sodium azide (4.70g) in degassed water (25ml) was added to a solution of (1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate (9.99g) in tetrahydrofuran (60ml) and stirred for 10 min. Tetrakis(triphenylphosphine)palladium(0) (365mg) was added and stirred for 10 min. The aqueous layer was separated and extracted twice with ethyl acetate. The combined organic layers were dried ($MgSO_4$), concentrated and purified on a short column (SiO_2, ethyl acetate:isohexane 1:2 as eluant) to afford a yellow oil. This was dissolved in tetrahydrofuran (25ml) and slowly added to a suspension of sodium hydride (2.94g, 60%

dispersion in oil) in tetrahydrofuran (60ml) at -78°C. A solution of ethyl bromoacetate (8.2ml) in tetrahydrofuran (5ml) was added and the mixture was allowed to warm to 20°C and stirred for 30 min. Aqueous ammonium chloride solution was added and the mixture was extracted with ether . The organic layers were dried ($MgSO_4$), concentrated and purified (SiO_2, ether:isohexane 1:5 as eluant) to afford a colourless oil. A solution of this oil and triphenylphosphine (17.89g) in tetrahydrofuran (90ml) was stirred for 10 min. Water (15ml) was added and the solution was stirred for 18 hours. The solvent was removed *in vacuo* and the residue azeotroped with toluene then purified (SiO_2, ethyl acetate then ethyl acetate - methanol - ammonia (90:9:1) as eluant) to afford a pale yellow oil (7.14g).

A solution of this compound in tetrahydrofuran (50ml) was added over 25 min to a solution of 4,6-dichloro-5-nitro-2-[(3,3,3-trifluoropropyl)thio] pyrimidine (prepared as described in International Patent Application WO 9703084) (24.8g) and *N,N*-diisopropylethylamine (77.5ml) in dry tetrahydrofuran (100ml) and then stirred for 30 minutes. Water was added and the mixture was extracted with ether (three times). The organic layers were dried ($MgSO_4$), concentrated and purified (SiO_2, ethyl acetate:isohexane 1:4 as eluant) to afford the subtitle compound (7.39g).

MS (APCI) 367/9 ($M-(EtO_2CCH_2O)^+$), 367 (100%)

b) (1*S*-*cis*) 2-[[4-[7-Chloro-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl]-2-cyclopenten-1-yl]oxy]-acetic acid, ethyl ester

Prepared according to the method of example 3, steps e) and f) using the product of step a).

MS (APCI) 348/50 ($M-(EtO_2CCH_2O)^+$), 348 (100%).

c) [1*S*-(*cis*)] 2-[[4-[7-Amino-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-2-cyclopenten-1-yl]oxy]-acetic acid, ethyl ester

Prepared according to the method of example 3, step g) using the product of step b).

MS (APCI) 433 ($M+H^+$, 100%).

d) [1*S*-(*cis*)] 2-[[4-[7-Amino-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-2-cyclopenten-1-yl]oxy]-1-ethanol

Prepared according to the method of example 3, step k) using the product of step c).

MS (APCI) 391 ($M+H^+$, 100%).

e) [3a*R*-(3aα,4α,6α,6aα)]-2-[6-[7-Amino-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-yloxy]ethanol

A solution of the product from step d) (454mg), osmium tetroxide (0.17ml of 0.1M solution in *t*-butanol), *N*-methylmorpholine *N*-oxide (210mg) and pyridine (0.09ml) in acetone (5ml) and water (1ml) was heated at 70°C for 5 hours. Sodium hydrosulfite (330mg) in water (1ml) was added, the solvent was remove *in vacuo* and the residue azeotroped with toluene. A solution of this and *p*-toluenesulfonic acid (50mg) in acetone (5ml) and 2,2-dimethoxypropane (2ml) was stirred for 3h. The solvent was remove *in vacuo,* aq sodium hydrogen carbonate solution added and the mixture was extracted with ethyl acetate. The organic layers were dried ($MgSO_4$), concentrated and purified (SiO_2,isohexane:acetone 5:2 as eluant) to afford the subtitle compound as a white solid (367mg).

MS (APCI) 465 ($M+H^+$, 100%)

f) [3a*R*-(3aα,4α,6α,6aα)]-2-[6-[7-Bromo-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-yloxy]ethanol

Prepared according to the method of Example 3, step i) using the product of step e).

MS (APCI) 528/30 ($M+H^+$), 528 (100%)

g) [3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]-2-[6-(7-Phenylcyclopropyl)amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-1,3-dioxol-4-yloxy]ethanol**

Prepared according to the method of Example 3, step j) using the product of step f) and (1*R-trans*)-2-phenyl-cyclopropanamine, [*R*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1) (prepared as described by L.A. Mitscher *et al.*, J. Med. Chem. 1986, **29**, 2044).

MS (APCI) 581 ($M+H^+$, 100%)

h) [1*S*-[1α,2α,3β,5β(1*S,2*R**)]]-3-(2-Hydroxyethoxy)-5-[7-(2-phenylcyclopropyl)amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-cyclopentane-1,2-diol**

Prepared according to the method of Example 1, step h) using the product of step g).

MS (APCI) 540 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 7.35-7.16 (5H, m), 4.97 (1H, q), 4.62-4.54 (1H, m), 3.98-3.92 (1H, m), 3.78-3.72 (1H, m), 3.55-3.44 (4H, m), 3.26-3.19 (2H, m), 3.16-3.07 (1H, m), 2.70-2.61 (1H, m), 2.58-2.52 (1H, m), 2.23-2.18 (1H, m), 2.05-1.97 (1H, m), 1.86 (1H, s), 1.54-1.46 (1H, m), 1.38-1.30 (1H, m).

Example 8

[1*S*-[1α,2β,3β,4α(1*S, 2*R**)]]-4-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-1,2,3-triol**

a) [3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]-6-[[7-[(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-ol**

The subtitle compound was prepared according to the method of Example 1, step e) using the product of Example 3, step f) and the product of example 2, step d).

MS (APCI) 519 ($M+H^+$, 100%).

b) [3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]]-6-[[7-[(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylsulfonyl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-ol**

The subtitle compound was prepared according to the method of Example 1, step f) using the product of step a).

MS (APCI) 551 ($M+H^+$, 100%).

c) [3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]]-6-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-ol**

The subtitle compound was prepared according to the method of Example 4, step c) using the product of step b).

MS (APCI) 533 ($M+H^+$, 100%)

d) [1*S*-[1α,2β,3β,4α(1*S, 2*R**)]]-4-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-1,2,3-triol**

The title compound was prepared according to the method of Example 1, step h) using the product of step c).

NMR δH (d_6-DMSO) 7.15-6.98 (3H, m), 6.67 (1H, s), 5.11-5.09 (1H, m), 4.82-4.76 (1H, m), 4.34-4.21 (3H, m), 3.7 (1H, s), 3.2-2.92 (4H, m), 2.77 (1H, m), 2.42-2.36 (1H, m), 2.2-2.18 (1H, m), 1.42-1.25 (6H, m), 0.9 (3H, q).

MS (APCI) 493 ($M+H^+$, 100%)

Example 9

[1*S*-[1α,2α,3β(1*S,2*R**),5β]]-3-[5-(Butylthio)-7-[(2-phenylcyclopropyl)amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxethoxy)-cyclopentane-1,2-diol**

a) [3a*S*-(3aα,4α,6α,6aα)]-[Tetrahydro-6-hydroxy-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-yl]-carbamic acid, phenylmethyl ester

Potassium carbonate (39.3g) was added to a suspension of [3α*R*-(3aα,4α,6α,6aα)]-6-amino-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-ol, hydrochloride, (prepared as described in WO 9905142) (27.1g) in 4-methyl-2-pentanone (500ml). Water (150ml) was then added followed by dropwise addition of benzyl chloroformate (23.1g). The reaction mixture was stirred at room temperature for 4 hours before the organic phase was separated. The aqueous phase was extracted with 4-methyl-2-pentanone (2x50ml). The combined organics were concentrated and the residue was purified (SiO_2, dichloromethane:methanol, 95:5 to 90:10 as eluant) to give the subtitle compound (39.23g).

NMR δH ($CDCl_3$) 7.32 (5H, m), 5.65 (1H, br s), 5.10 (2H, br s), 4.59 (1H, d), 4.48 (1H. d), 4.27 (1H, m), 4.19 (1H, br m), 2.24 (1H, br s), 1.69 (1H, d), 1.41 (3H, s), 1.26 (3H, s).

b) [3a*S*-(3aα,4α,6α,6aα)]-[2,2-Dimethyl-6-(2-hydroxyethoxy)-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-yl]-carbamic acid, phenylmethyl ester

Potassium *tert*-butoxide (3.6g) in tetrahydrofuran (20ml) was added over 5 minutes to a solution of the product from step a) (39.23g) in tetrahydrofuran (200ml). After 15 minutes, ethyl bromoacetate (3.7ml) in tetrahydrofuran (10ml) was added dropwise. The mixture was stirred at 0°C for 10 minutes, then further ethyl bromoacetate was added (3.7ml x4). The reaction mixture was stirred at 0°C a further 2 hours. Lithium borohydride (2.79g) was then added portionwise to the resulting suspension and the reaction mixture was stirred at <5°C for 16 hours. Glacial acetic acid (23g) was added dropwise to the cold mixture. After stirring for 30 minutes, water (100ml) was added dropwise and the resulting mixture was stirred for 30 minutes. The phases were then separated and the aqueous phase was extracted with ethyl acetate. The combined organics were washed with saturated sodium bicarbonate and brine, dried and concentrated. The residue was purified (SiO_2, ethyl acetate:hexane, 25:75 to 50:50 as eluant) to give the subtitle compound (38.6g).

MS (APCI) 218 ($M+H^+$, 100%).

c)) [3a*R*-(3aα,4α,6α,6aα)]-2-[[6-Amino-2,2-dimethyl-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-yl]oxy]-ethanol

A slurry of 5% palladium on charcoal (4g) in ethanol was added to a solution of the product from step b) (39.96g) in ethanol (250ml) and the mixture was hydrogenated at 1.2 bar for 20 hours. The catalyst was filtered off and the filtrate was concentrated to give the subtitle compound (23.65g).

MS (APCI) 160 ($M+H^+$, 100%).

d) 2-(Butylthio)-4,6-dichloropyrimidine-5-amine

The subtitle compound was prepared according to the method of example 3, step e) using 2-(butylthio)-4,6-dichloro-5-nitro-pyrimidine (prepared as described in DE 2223644).

NMR δH ($CDCl_3$) 4.20 (2H, br s), 3.10 (2H, t), 1.70 (2H, m), 1.47 (2H, m), 0.95 (3H, t).

e) [3a*R*-(3aα,4α,6α,6aα)]-2-[[6-[[5-Amino-2-(butylthio)-6-chloro-pyrimidin-4-yl]amino]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-yl]oxy]ethanol

The subtitle compound was prepared according to the method of example 3, step d) using the products of steps c) and d).

MS (APCI) 433 ($M+H^+$, 100%).

f) [3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]]-2-[6-[[5-(Butylthio)-7-chloro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-yl]oxy]-ethanol**

The subtitle compound was prepared according to the method of Example 3, step f) using the product of step e).

NMR δH ($CDCl_3$) 5.53 (1H, m), 5.21 (1H, m), 4.88 (1H, d), 4.05 (1H, m), 3.59 (4H, m), 3.24 (2H, t), 2.70 (1H, m), 2.53 (1H, m), 2.13 (1H, t), 1.79 (2H, m), 1.55 (5H, m), 1.37 (3H, s), 0.98 (3H, t).

g) [3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]]-2-[6-[[5-(Butylthio)-7-[2-phenylcyclopropyl]amino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-yl]oxy]-ethanol**

The subtitle compound was prepared according to the method of Example 3, step j) using the product of step f).

MS (APCI) 541 ($M+H^+$, 100%).

h) [1*S*-[1α,2α,3β(1*S,2*R**),5β]]-3-[5-(Butylthio)-7-[(2-phenylcyclopropyl)amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxethoxy)-cyclopentane-1,2-diol**

The title compound was prepared according to the method of example 1, step h) using the product of step g).

MS (APCI) 501 ($M+H^+$, 100%)

NMR δH (d_6-DMSO) 9.33 (1H, d), 7.30 (2H, m), 7.18 (3H, m), 5.12 (1H, d), 5.04 (1H, d), 4.96 (1H, q), 4.59 (2H, m), 3.94 (1H, s), 3.76 (1H, m), 3.51 (4H, m), 3.22 (1H, m), 2.98 (1H, m), 2.86 (1H, m), 2.65 (1H, m), 2.14 (1H, m), 2.05 (1H, m), 1.21-1.53 (6H, m), 0.80 (3H, t).

Pharmacological data

The preparation for the assay of the P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) receptor agonist/antagonist activity in washed human platelets for the compounds of the invention was carried out as follows.

Human venous blood (100 ml) was divided equally between 3 tubes, each containing 3.2% trisodium citrate (4 ml) as anti-coagulant. The tubes were centrifuged for 15 minutes at 240G to obtain a platelet-rich plasma (PRP) to which 300 ng/ml prostacyclin was added to stabilize the platelets during the washing procedure. Red cell free PRP was obtained by centrifugation for 10 minutes at 125G followed by further centrifugation for 15 minutes at 640G. The supernatant was discarded and the platelet pellet resuspended in modified, Calcium Free Tyrode solution (10 ml) (CFT), composition: NaCl 137mM, $NaHCO_3$ 11.9mM, NaH_2PO_4 0.4mM, KCl 2.7 mM, $MgCl_2$ 1.1 mM, dextrose 5.6 mM, gassed with 95% O_2/5% CO_2 and maintained at 37°C. Following addition of a further 300 ng/ml PGI_2, the pooled suspension was centrifuged once more for 15 minutes at 640G. The supernatant was discarded and the platelets resuspended initially in 10 ml CFT with further CFT added to adjust the final platelet count to $2x10^5$/ml. This final suspension was stored in a 60 ml syringe at 3°C with air excluded. To allow recovery from PGI_2-inhibition of normal function, platelets were used in aggregation studies no sooner than 2 hours after final resuspension.

In all studies, 3 ml aliquots of platelet suspension were added to tubes containing $CaCl_2$ solution (60 µl of 50 mM solution with a final concentration of 1mM). Human fibrinogen (Sigma, F 4883) and 8-sulphophenyltheophylline (8-SPT which was used to block any P_1-agonist activity of compounds) were added to give final concentrations of 0.2 mg/ml (60 µl of 10 mg/ml solution of clottable protein in saline) and 300 nM (10 µl of 15 mM solution in 6% glucose), respectively. Platelets or buffer as appropriate were added in a volume of 150 µl to the individual wells of a 96 well plate. All measurements were made in triplicate in platelets from each donor.

The agonist/antagonist potency was assessed as follows.

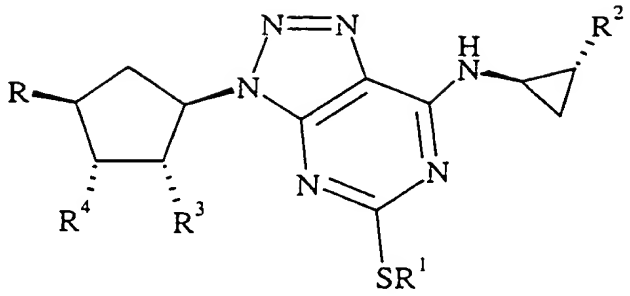
Aggregation responses in 96 well plates were measured using the change in absorbance given by the plate reader at 660 nm. Either a Bio-Tec Ceres 900C or a Dynatech MRX were used as the plate reader.

The absorbance of each well in the plate was read at 660 nm to establish a baseline figure. Saline or the appropriate solution of test compound was added to each well in a volume of 10 µl to give a final concentration of 0, 0.01, 0.1, 1, 10 or 100 mM. The plate was then shaken for 5 min on an orbital shaker on setting 10 and the absorbance read at 660 nm. Aggregation at this point was indicative of agonist activity of the test compound. Saline or ADP (30 mM; 10 µl of 450 mM) was then added to each well and the plate shaken for a further 5 min before reading the absorbance again at 660 nm.

Antagonist potency was estimated as a % inhibition of the control ADP response to obtain an IC_{50}. Compounds exemplified have pIC_{50} values of more than 5.0.

Claims

1. A compound of formula (I)



(I)

wherein:

R^1 is C_{3-5} alkyl optionally substituted by one or more halogen atoms;

R^2 is a phenyl group, optionally substituted by one or more fluorine atoms;

R^3 and R^4 are both hydroxy;

R is XOH, where X is CH_2, OCH_2CH_2 or a bond;

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt

provided that:

when X is CH_2 or a bond, R^1 is not propyl.

when X is CH_2 and R^1 is $CH_2CH_2CF_3$, butyl or pentyl, the phenyl group at R^2 must be substituted by fluorine.

when X is OCH_2CH_2 and R^1 is propyl, the phenyl group at R^2 must be substituted by fluorine.

2. A compound according to claim 1 in which R^1 is 3,3,3,-trifluoropropyl, butyl or propyl.

3. A compound according to claims 1 or 2 in which R^2 is phenyl or 4-fluorophenyl or 3,4-difluorophenyl.

4. A compound according to any one of claims 1 to 3 in which R is CH_2OH or OCH_2CH_2OH.

5. A compound according to claim 1 which is:

[1*R*-[1α,2α,3β(1*R**,2*S**),5β]]-3-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol;

[1*R*-[1α,2α,3β(1*R**,2*S**),5β]]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol;

[1*S*-(1α, 2α, 3β (1*S**,2*R**),5β]]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol;

[1*R*-[1α,2α,3β(1*R**,2*S**),5β]]-3-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol;

[1*S*-[1α,2β,3β,4α(1*S**,2*R**)]]-4-[5-(Butylthio)-7-[[2-(4-fluorophenyl)cyclopropyl]amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-cyclopentane-1,2,3-triol;

[1*S*-(1α,2α,3β(1*S**,2*R**),5β)]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol;

[1*S*-[1α,2α,3β,5β(1*S**,2*R**)]]-3-(2-Hydroxyethoxy)-5-[7-(2-phenylcyclopropyl)amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-cyclopentane-1,2-diol

[1*S*-[1α,2β,3β,4α(1*S**, 2*R**)]]-4-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-1,2,3-triol;

[1*S*-[1α,2α,3β(1*S**,2*R**),5β]]-3-[5-(Butylthio)-7-[(2-phenylcyclopropyl)amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxethoxy)-cyclopentane-1,2-diol;

or pharmaceutically acceptable salts or solvates thereof, or solvates of such salts.

6. A pharmaceutical composition comprising a compound according to any one of claims 1 to 5 in combination with a pharmaceutically acceptable diluent, adjuvent and/or carrier.

7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 5 for use in the treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, and/or peripheral vascular disease.

8. A pharmaceutical composition comprising a compound according to any one of claims 1 to 5 for use in the treatment or prevention of unstable or stable angina.

9. A compound according to any one of claims 1 to 5 for use in therapy.

10. A compound according to any one of claims 1 to 5 for use in the treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, and/or peripheral vascular disease.

11. A compound according to any one of claims 1 to 5 for use in the treatment or prevention of unstable or stable angina.

12. The use of a compound according to any one of claims 1 to 5 as an active ingredient in the manufacture of a medicament for use in the treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, and/or peripheral vascular disease.

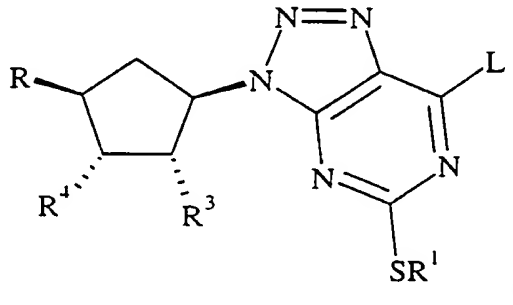
13. The use of a compound according to any one of claims 1 to 5 as an active ingredient in the manufacture of a medicament for use in the treatment or prevention of unstable or stable angina

14. A method of treatment or prevention of a platelet aggregation disorder which comprises administering to a person suffering from or susceptible to such a disorder a therapeutically effective amount of a compound according to any one of claims 1 to 5.

15. A method of treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, and/or peripheral vascular disease, which comprises administering to a person suffering from or susceptible to such a condition a therapeutically effective amount of a compound according to any one of claims 1 to 5.

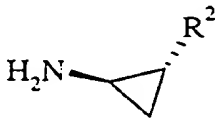
16. A method of treatment or prevention of unstable or stable angina which comprises administering to a person suffering from or susceptible to such a condition a therapeutically effective amount of a compound according to any one of claims 1 to 5.

17. A process for the preparation of a compound of formula (I) which comprises reacting a compound of formula (II):



(II)

where R, R^1, R^3 and R^4 are as defined in claim 1, or are protected derivatives thereof, or R^3 and R^4 together form a bond in the 5-membered ring, or R is CH_2CH_2OR' where R' is C_{1-6} alkyl or benzyl, and L is a leaving group,
with a compound of formula (III):



(III)

where R^2 is defined in claim 1 or is a protected derivative thereof,
in the presence of a base in an inert solvent at ambient or elevated temperature,
and optionally thereafter and in any order:

converting one or more functional groups into further functional groups;

removing any protecting groups;

forming a pharmaceutically acceptable salt or solvate, or a solvate of such a salt.

18. The compounds:

[3a*R*-[3aα,4α,6α(1*R**,2*S**),6aα]]-6-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-(propylsulphonyl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol;

[[3a*R*-[3aα,4α,6α(1*R**,2*S**),6aα]]-6-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropy)lthio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol;

[3a*R*-[3aα,4α,6α(1*R**,2*S**),6aα]-6-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol;

[3a*R*-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-ol;

[3a*R*-(3aα,4α,6α,6aα)]-[[6-[7-Amino-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-ol]oxy]acetic acid, methyl ester;

[3a*R*-(3aα,4α,6α,6aα)]-[[6-[7-Bromo-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-ol]oxy]acetic acid, methyl ester;

[3a*R*-[3aα,4α,6α(1*R**,2*S**),6aα]]-[[6-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-yl]oxy]acetic acid, methyl ester;

[3a*R*-[3aα,4α,6α(1*R**,2*S**),6aα]]-6-[[7-[2-(3,4-Difluorophenyl) cyclopropyl]amino-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-yl]oxy]-ethanol;

[3a*R*-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol;

[3a*R*-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(propylsulfonyl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol;

[3a*R*-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(butylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol;

[3a*R*-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(butylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol, acetate;

[3a*R*-(3aα,4α,6α,6aα)]-6-[7-Bromo-5-(butylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol, acetate;

[3a*R*-[3aα,4α,6α(1*R**,2*S**),6aα]]-6-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol, acetate;

[3a*R*-[3aα,4α,6α,6aα(1*S**,2*R**)]]-6-[7-[[(4-Fluorophenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-ol;

[3a*R*-[3aα,4α,6α,6aα(1*S**,2*R**)]]-6-[[7-[(4-Fluorophenyl)cyclopropyl]amino]-5-(propylsulphonyl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-ol;

[3a*R*-[3aα,4α,6α,6aα(1*S**,2*R**)]]-6-[7-[[(4-Fluorophenyl)cyclopropyl]amino]-5-(butylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-ol;

[1*S*-(1α,2α,3β(1*S**,2*R**),5β)]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylsulphonyl)-3*H*-1,2,3-triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol;

(1*S*-*cis*)-2-[[4-[[6-Chloro-5-nitro-2-[(3,3,3-trifluoropropyl)thio]-4-pyrimidinyl]amino]-2-cyclopenten-1-yl]oxy]-acetic acid, ethyl ester;

(1*S*-*cis*) 2-[[4-[7-Chloro-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl]-2-cyclopenten-1-yl]oxy]-acetic acid, ethyl ester;

[1*S*-(*cis*)] 2-[[4-[7-Amino-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-2-cyclopenten-1-yl]oxy]-acetic acid, ethyl ester;

[1*S*-(*cis*)] 2-[[4-[7-Amino-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-2-cyclopenten-1-yl]oxy]-1-ethanol;

[3a*R*-(3aα,4α,6α,6aα)]-2-[6-[7-Amino-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-yloxy]ethanol;

[3a*R*-(3aα,4α,6α,6aα)]-2-[6-[7-Bromo-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-yloxy]ethanol;

[3a*R*-[3aα,4α,6α(1*R**,2*S**),6aα]-2-[6-(7-Phenylcyclopropyl)amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-1,3-dioxol-4-yloxy]ethanol;

[3a*R*-[3aα,4α,6α(1*R**,2*S**),6aα]-6-[[7-[(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-ol;

[3a*R*-[3aα,4α,6α(1*R**,2*S**),6aα]]-6-[[7-[(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylsulfonyl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-ol;

[3a*R*-[3aα,4α,6α(1*R**,2*S**),6aα]]-6-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-ol;

[3a*S*-(3aα,4α,6α,6aα)]-[Tetrahydro-6-hydroxy-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-yl]-carbamic acid, phenylmethyl ester;

[3a*S*-(3aα,4α,6α,6aα)]-[2,2-Dimethyl-6-(2-hydroxyethoxy)-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-yl]-carbamic acid, phenylmethyl ester;

[3a*R*-(3aα,4α,6α,6aα)]-2-[[6-Amino-2,2-dimethyl-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-yl]oxy]-ethanol;

2-(Butylthio)-4,6-dichloropyrimidine-5-amine;

[3a*R*-(3aα,4α,6α,6aα)]-2-[[6-[[5-Amino-2-(butylthio)-6-chloro-pyrimidin-4-yl]amino]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-yl]oxy]ethanol;

[3a*R*-[3aα,4α,6α(1*R**,2*S**),6aα]]-2-[6-[[5-(Butylthio)-7-chloro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-yl]oxy]-ethanol;

[3a*R*-[3aα,4α,6α(1*R**,2*S**),6aα]]-2-[6-[[5-(Butylthio)-7-[2-phenylcyclopropyl]amino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-yl]oxy]-ethanol.

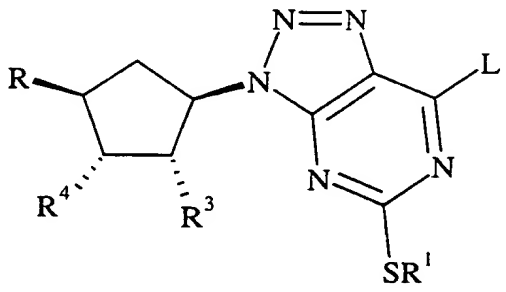
AMENDED CLAIMS

[received by the International Bureau on 02 May 2000 (02.05.00);
original claim 18 amended; new claims 19-21 added; remaining claims unchanged (2 pages)]

[3a*R*-[3aα,4α,6α(1*R**,2*S**),6aα]]-2-[6-[[5-(Butylthio)-7-[2-phenylcyclopropyl]amino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-yl]oxy]-ethanol.

[3a*R*-(3aα,4α,6α,6aα)]-6-[[6-Chloro-5-nitro-2-(propylthio)-pyrimidin-4-yl]amino]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-ol

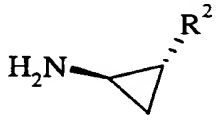
19. A compound of formula (II):



(II)

where R, R^1, R^3 and R^4 are as defined in claim 1, or are protected derivatives thereof, or R^3 and R^4 together form a bond in the 5-membered ring, or R is CH_2CH_2OR' where R' is C_{1-6} alkyl or benzyl, and L is a leaving group.

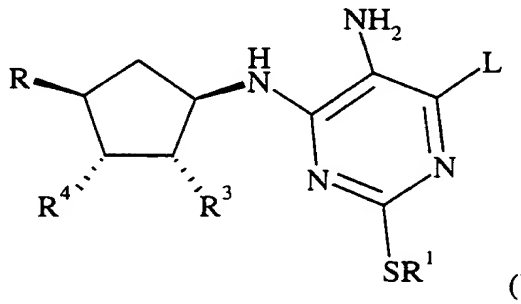
20. A compound of formula (III):



(III)

where R^2 is as defined in claim 1, or is a protected derivative thereof.

21. A compound of formula (V):



(V)

wherein R^1 is as defined in claim 1, and R is as defined in claim 1, or is a protected derivative thereof, or is OCH_2CO_2R', where R' is C_{1-6} alkyl or benzyl, and L is as defined above and R^3 and R^4 are as defined in claim 1 or are protected derivatives thereof or R^3 and R^4 together form a bond in the 5-membered ring.

INTERNATIONAL SEARCH REPORT

Int. [redacted]onal application No.
PCT/SE 99/02256

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 487/04, A61K 31/519, A61K 31/4192, A61P 7/02, A61P 9/10
// (C07D 487/04, 249:00, 239:00)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 9905143 A1 (ASTRA PHARMACEUTICALS LTD.), 4 February 1999 (04.02.99) --	1-18
A	WO 9828300 A1 (ASTRA PHARMACEUTICALS LTD.), 2 July 1998 (02.07.98) --	1-18
A	DE 2223644 A (CIBA-GEIGY AG), 30 November 1972 (30.11.72) -- --------	18

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 March 2000	18 April 2000 (18.04.00)
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/02256

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 14-16
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see next sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Box I.1

Claims 14-16 relate to a methods of treatment of the human or animal body by surgery or by therapy. See PCT, Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/composition.

Box II

In order to fulfil the requirements of unity of invention, it is necessary that the intermediate compounds according to claim 18 are closely interconnected with the end products of formula (I) as well as with themselves. Such close connection requires that the essential structural part of the end product is incorporated by the intermediate. However, the present application lacks a single general inventive concept based on the above principle. This leads to the presence of at least the subjects listed below, each falling under its own restricted inventive concept.

1. Claims 1-17 concerning triazolo[4,5-d]pyrimidine compounds of formula I for pharmaceutical use, pharmaceutical compositions containing the compounds, a process for their preparation and claim 18 in part concerning compounds containing the main group 1,2,3-triazolo[4,5-d]pyrimidin-3-yl, useful as intermediates for the process of preparation.

2. Claim 18 in part concerning compounds, such as(1S-*cis*)-2-[[4-[[6-Chloro-5-nitro-2-[(3,3,3-trifluoropropyl)thio]-4-pyrimidinyl]-amino]2-cyclopenten-1yl]oxy]-acetic acid, ethyl ester or 3a*R*-(3aα,4α,6α,6aα)]-2-[[6-[[5-Amino-2-(butylthio)-6-chloro-pyrimidin-4-yl]amino]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-yl]-oxy]-ethanol, useful as intermediates.

3. Claim 18 in part concerning compounds, such as [3a*S*-(3aα,4α,6α,6aα)]-[Tetrahydro-6-hydroxy-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-yl]-carbamic acid, phenylmethyl ester or [3a*S*-(3aα,4α,6α,6aα)]-[2,2-Dimethyl-6-(2-hydroxyethoxy)-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-yl]-carbamic acid, phenylmethyl ester, useful as intermediates.

4. Claim 18 in part concerning compounds, such as 3a*R*-(3aα,4α,6α,6aα)]-2-[6-Amino-[2,2-dimethyl-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-yl]-oxy]-ethanol, useful as intermediates.

5. Claim 18 in part concerning compounds, such as 2-(Butylthio)-4,6-dichloropyrimidine-5-amine, useful as intermediates.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 99/02256

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9905143 A1	04/02/99	AU 8370698 A	16/02/99
		SE 9702773 D	00/00/00
		SE 9702775 D	00/00/00
WO 9828300 A1	02/07/98	AU 5501598 A	17/07/98
		EP 0946561 A	06/10/99
		SE 9604787 D	00/00/00
		SE 9604788 D	00/00/00
DE 2223644 A	30/11/72	BG 19073 A	30/04/75
		BR 7203098 D	00/00/00
		CA 994773 A	10/08/76
		CH 558137 A	31/01/75
		CS 177082 B	29/07/77
		EG 10574 A	31/01/76
		ES 402755 A	01/04/75
		FR 2137933 A	29/12/72
		GB 1393993 A	14/05/75
		IL 39417 A	28/07/75
		IT 955556 B	29/09/73
		JP 56054283 B	24/12/81
		NL 7206602 A	21/11/72
		TR 17050 A	25/04/74
		US 3926997 A	16/12/75
		US 3969101 A	13/07/76
		ZA 7203325 A	28/02/73

US 09/508 195
5000

Copy for the designated Office (DO/US) PCT/SE99/02256

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

ASTRAZENECA
Global Intellectual Property
P.O. Box 272
Mereside, Alderley Park
Macclesfield
Cheshire, SK10 4GR
ROYAUME-UNI

Date of mailing (day/month/year)
26 July 2000 (26.07.00)

Applicant's or agent's file reference
F 2049-1 WO

IMPORTANT NOTIFICATION

International application No.
PCT/SE99/02256

International filing date (day/month/year)
02 December 1999 (02.12.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
ASTRAZENECA UK LIMITED
15 Stanhope Gate
London W1Y 6LN
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [X] the name [X] the address [X] the nationality [X] the residence

Name and Address
ASTRAZENECA AB
S-151 85 Södertälje
Sweden

State of Nationality: SE
State of Residence: SE
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:
The first named applicant has assigned all his rights to ASTRAZENECA AB, which shall now be recorded as applicant for all designated States except the United States of America.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Beate Giffo-Schmitt
Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

ASTRAZENECA
Global Intellectual Property
P.O. Box 272
Mereside, Alderley Park
Macclesfield
Cheshire, SK10 4GR
ROYAUME-UNI

Date of mailing (day/month/year)
26 July 2000 (26.07.00)

Applicant's or agent's file reference
F 2049-1 WO

IMPORTANT NOTIFICATION

International application No.
PCT/SE99/02256

International filing date (day/month/year)
02 December 1999 (02.12.99)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address

ASTRAZENECA AB
Intellectual Property, Patents
S-151 85 Södertälje
Sweden

State of Nationality

State of Residence

Telephone No.
46 8 553 260 00

Facsimile No.
46 8 553 288 20

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address

ASTRAZENECA
Global Intellectual Property
P.O. Box 272
Mereside, Alderley Park
Macclesfield
Cheshire, SK10 4GR
United Kingdom

State of Nationality

State of Residence

Telephone No.
0044-1625-58 28 28

Facsimile No.
0044-1625 58 30 74

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Beate Giffo-Schmitt

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

09/508195

PCT

From the INTERNATIONAL BUREAU

To:

ASTRAZENECA AB
Intellectual Property, Patents
S-151 85 Södertälje
SUÈDE

5000

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 24 March 2000 (24.03.00)	
Applicant's or agent's file reference F 2049-1 WO	**IMPORTANT NOTIFICATION**
International application No. PCT/SE99/02256	**International filing date** (day/month/year) 02 December 1999 (02.12.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
ASTRA AKTIEBOLAG S-151 85 Södertälje Sweden	SE	SE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
ASTRAZENECA AB S-151 85 Södertälje Sweden	SE	SE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer C. Cupello
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

ASTRAZENECA AB
Intellectual Property, Patents
S-151 85 Södertälje
SUÈDE

Date of mailing (day/month/year)
24 March 2000 (24.03.00)

Applicant's or agent's file reference
F 2049-1 WO

IMPORTANT NOTIFICATION

International application No.
PCT/SE99/02256

International filing date (day/month/year)
02 December 1999 (02.12.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
ASTRA PHARMACEUTICALS LTD.
Home Park
Kings Langley
Herts WD4 8DH
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
ASTRAZENECA UK LIMITED
15 Stanhope Gate
London W1Y 6LN
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
C. Cupello
Telephone No.: (41-22) 338.83.38

09/009195
16C3

PATENT COOPERATION TREATY

REC'D 21 FEB 2001
WIPO PCT

PCT

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APR 18 2001
TECH CENTER 1600/2900

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
F.2049-iWO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE99/02256	02/12/1999	04/12/1998
International Patent Classification (IPC) or national classification and IPC C07D487/04		
Applicant ASTRAZENECA AB (UK LIMITED) et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14/06/2000	19.02.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Stroeter, T Telephone No. +49 89 2399 8088

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/SE99/02256

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-43	as originally filed

Claims, No.:

1-17,18 (part)	as originally filed
18 (part),19-21	as amended under Article 19

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 14-16, 19-21.

because:

   ☒ the said international application, or the said claims Nos. 14-16 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 19-21.

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:
see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-18.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-17, 18(part)
	No:	Claims	18(part)
Industrial applicability (IA)	Yes:	Claims	1-13, 17, 18
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 14 to 16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

New claims 19 to 21 as received by the International Bureau on 02.05.2000 **will not be considered in the examination stated under item V**, because the subject-matter of said claims had not been searched. Amended claim 18 which contains one additional compound, however, is accepted.

Re Item IV

Lack of unity of invention

Remark: Present claim 18 contains a list of 36 compounds which were numbered according to the order of their appearance in said claim in order to simplify their assignment to the different groups of inventions as follows.

The separate inventions are:

group I: claims 1 to 17, 18 (compounds 1-18, 20-28, 34 and 35) and 19, each in part drawn to compounds having triazolo[4,5-d]pyrimidine as a common structural feature and a substituent R which is $-CH_2OH$, $-OCH_2CH_2OH$ or -OH or a derivative group thereof.

group II: claim 18 (compounds 19, 33 and 36) in part and 21, drawn to compounds having pyrimidine as the main common structural feature.

group III: claim 18 (compounds 29-31) in part, drawn to compounds having tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol as the main common structural feature.

group IV: claim 18 in part, drawn to compound 2-butylthio-4,6-dichloropyrimidine- 5-amine (compound 32).

The subject-matter of claims 19 to 21 and **group V** (claim 20, drawn to cyclopropane amines of formula (III)) as cited in the "Invitation to restrict or to pay additional fees" with the communication of 25.08.00) will not be considered for the present examination as mentioned in **item III** and the remark on sheet 2 of said communication.

The additional tax paid for the invention of **group V** was repaid to the Applicant since only **4 inventions** were thus examined.

These inventions are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

As can be taken from prior art document WO-A-98 28300 which is mentioned in the International Search Report, compounds are known which show the same parental structure as the compounds of present claim 1 and which are substituted similarly with the exception of R.

To give an example, claim 5 of said document, line 3-4, mentions [1S-[1α, 2β, 3β, 4α (trans)]]-2,3-dihydroxy-4-[7-[(2-phenylcyclopropyl)amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]cyclopentanecarboxylic acid (comparison to formula (I): R^1 = propyl, R^2 = phenyl, R^3, R^4 = OH). However, it is acknowledged in favour of the Applicant that the compounds of **group I** are unified due to the selection of hydroxylic substituents for R.

The intermediates of **groups II to V**, however, are not closely related to the structure of the compounds of **group I** (because they do not contain a large, essential portion of said structure) as well as with themselves. The subject-matter of each of said groups is not linked via a common structural feature that defines a novel and inventive contribution over the prior art and as such refers to different inventions.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Prior art documents

Reference is made to the following documents. The given numbering will be adhered to in the rest of the procedure:

D1: WO-A1-9905143
D2: WO-A1-9828300
D3: DE-A-2223644

D1 and D2 reveal compounds which are structurally related to those of the present application and are also active as P_{2T} antagonists. D3 discloses compounds with a different parental system and furthermore relates to a different technical field. Concerning D1 please also see section VI.

2 Novelty (Article 33(2) PCT)

The subject-matter of **group I** and of **groups II and III** is considered novel according to Article 33(2) PCT over the closest prior art D2 due to the presence of substituent R which is CH_2OH, $-OCH_2CH_2OH$ or -OH or a derivative group thereof. The compound of **group IV** has not been mentioned either in said document.

3 Inventive step (Article 33(3) PCT)

3.1 group I:

By revealing the compounds of formula (I), the present application gives a non-obvious solution to the problem of how to provide further compounds being active as P_{2T} antagonists.

The presence of substituent R with the specification given in present **claim 1** is regarded as a major structural difference to the compounds of closest prior art document D2 which bear acylic groups (COOH or $CONHR^3$). Thus, it could not be foreseen by the skilled man that the compounds of **claim 1** would be active as described and therefore, the claims in question are to be seen as involving an inventive step.

Therefore, **claim 1** and further **claims 2 to 17**, referring to the compounds of claim 1 and compounds 1-18, 20-28, 34 and 35 of **claim 18** which are intermediates covering a large part of the structure of said inventive compounds of present claim 1 are inventive by consequence and thus fulfil the requirements of Article 33(3) PCT.

3.2 **groups II, III and IV:**

The compounds 19, 29-33 and 36 claimed in part of claim 18 (groups II, III and IV) are intermediates which lack a close structural relation to the end-products of **claim 1**. In order to be inventive such intermediates should make a structural contribution to the subsequent product and the structural contribution provided by the intermediate should display at least one of those features which differentiate the subsequent product from known compounds in the prior art which does not appear to be the case here. Therefore said compounds are not inventive according to Article 33(3) PCT.

4 Industrial applicability (Article 33(4) PCT)

The subject-matter of the present **claims 1 to 13, 17 and 18** is in accordance with the requirements of Article 33(4) PCT.

For the assessment of the present **claims 14 to 16** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims.

The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

The International Search Report mentions one P-document D1, which does not form part of the state of the art according to Rule 64.1(b) PCT.

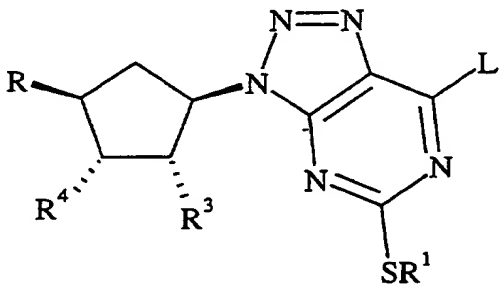
Re Item VIII
Certain observations on the international application

The sentence of line 4 on page 13 of the present description ("All novel ... invention") should be deleted, since it renders the scope of protection for the present invention unclear and leads to inconsistency between the present description and the present claims.

[3a*R*-[3aα,4α,6α(1*R**,2*S**),6aα]]-2-[6-[[5-(Butylthio)-7-[2-phenylcyclopropyl]amino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-yl]oxy]-ethanol.

[3a*R*-(3aα,4α,6α,6aα)]-6-[[6-Chloro-5-nitro-2-(propylthio)-pyrimidin-4-yl]amino]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-ol

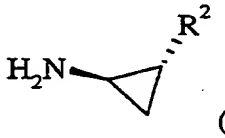
19. A compound of formula (II):



(II)

where R, R^1, R^3 and R^4 are as defined in claim 1, or are protected derivatives thereof, or R^3 and R^4 together form a bond in the 5-membered ring, or R is CH_2CH_2OR' where R' is C_{1-6} alkyl or benzyl, and L is a leaving group.

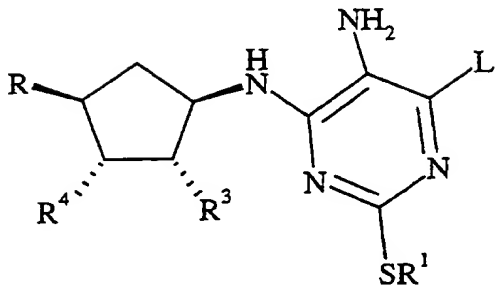
20. A compound of formula (III):



(III)

where R^2 is as defined in claim 1, or is a protected derivative thereof.

21. A compound of formula (V):



(V)

wherein R^1 is as defined in claim 1, and R is as defined in claim 1, or is a protected derivative thereof, or is OCH_2CO_2R', where R' is C_{1-6} alkyl or benzyl, and L is as defined above and R^3 and R^4 are as defined in claim 1 or are protected derivatives thereof or R^3 and R^4 together form a bond in the 5-membered ring.